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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,720	12/30/2003	Philip Jordan Thomas	UTSD:703USD1	7522

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EXAMINER	
RIGGINS, PATRICK S	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 09/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/748,720	THOMAS ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/25/05*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Receipt is acknowledged of an Amendment received 5/25/05. In this amendment sequence rules have been complied with in the specification, and claim 44 has been amended. Presently claims 44-57 are pending and under examination.

Priority

2. The instant claims are drawn to a "method of assessing protein stability, folding, and/or solubility". The limitation of "stability" was added to the claims with the Preliminary Amendment filed concurrently with the instant application on 12/30/03. This application was filed as a Divisional of 09/775,051, filed 1/31/01, now U.S. Patent 6,727,070 (hereinafter referred to as the parent), and as such can have no new matter added that was not a part of the originally filed disclosure. No support can be found in the originally filed specification, claims, or drawings of the parent. In all instances through out the disclosure, any reference to the assay of the invention only mentions "folding and/or solubility" (See page 2, line 9; page 3, lines 15-16; page 4, lines 15 and 24; page 5, lines 21-22 and 24-25; page 6, lines 5, 8, and 18; page 7, line 31; page 56, lines 11, 23 and 24; page 57, lines 9, 14, and 30; page 58, lines 19 and 23; page 61, line 3; the originally filed claims; and the title).

3. Only two references to protein stability could be found and neither of these was in reference to performing the assay of the invention. On page 68, lines 13-15 the specification states that the poor solubility of the CFTR fusions could be due to "limited solubility... or to marginal stability/misfolding or both." The next line then states that several mutations in the domain prevent its proper folding. Thus, the ultimate conclusion at this point would appear to be

that the poor solubility is due to improper folding. The other reference to stability can be found on page 69, line 20-23 which states that in this case the solubility of the MBP/α fusions is found to agree with "previously published stability and folding yield of these mutants without the α-fragment marker". The ultimate conclusion here is that the a-fragment "does not significantly impact the overall solubility characteristics of the MBP fusion proteins and is therefore a good reporter for protein solubility" (page 69, lines 23-25). It is noted also that in neither of these references to stability in the specification, was the discussion about the assay of the invention. Rather, they were both in reference to the creating of reagents for the assay. Indeed the whole purpose of this section of the specification appears to have been to ensure that the reagents designed would be suitable for the assay. In this regard, the beginning of the paragraph with the second instance of a mention of stability states: "To verify the hypothesis that the intensity of blue color on indicator plates is reporting target protein solubility, the amount of soluble versus insoluble protein was measure in biochemical fractionation experiments" (page 69, lines 11-13).

4. From all of this it is clear that at the time of original filing, i.e. 1/31/01, the applicants had only contemplated using the assay of their invention for determining protein folding and/or solubility. As such, any claim with a reference to measuring stability only receives the filing date of the instant application. Thus claims 44-57 are granted the priority date of 12/30/03.

Oath/Declaration

5. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

> The oath or declaration is defective because:
> The specification to which the oath or declaration is directed has not been adequately identified. See MPEP § 602.

As stated above the claims of the instant application are drawn to subject matter not disclose or apparently contemplated in the parent application. As such a new oath/declaration is required that properly references the instant application.

Specification

6. The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the following is required: References to the assay must be amended to reflect the claimed subject matter that the method is for assessing "protein stability, folding, and/or solubility".

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 44-57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a NEW MATTER rejection. This is a NEW REJECTION, necessitated by applicant's amendment on 5/25/05.

9. Claim 44 has been amended to enter the phrase "has only systemic effects on". No reference to systemic effects could be found anywhere in the originally filed specification, drawing, or claims. As such, this amendment constitutes the introduction of impermissible new matter.

10. It is noted, that it would appear that this amendment may have been intended to read -- has only systematic effects-- which does have proper support in the specification.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 44-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claim 44 recites that the "first segment has on systemic effects". As there is no reference to "systemic effects" in the specification and thus no proper definition of what is intended by this limitation, the skilled artisan would not be able to properly determine the metes and bound of this limitation in the claims. This is a NEW REJECTION necessitated by applicants' amendment to the claims on 5/25/05.

14. Claim 51 recites that the chromophore can be luciferase. As luciferase is not a chromophore, but is instead an enzyme, the skilled artisan could not ascertain the metes and bounds of this claim. This is a NEW REJECTION.

15. Claim 53 recites that the enzyme can be cytochrome c or chymotrypsin inhibitor. As neither of these molecules is an enzyme this claim does not appropriate delineate its metes and bounds. This is a NEW REJECTION.

16. Claims 53 and 56 both present lists in improper format. Both claims recite that the "enzyme" or "protein of interest" "is a number of possibilities where the list ends inclusively with "and". It is thus unclear, how a single enzyme or protein of interest could simultaneously be each of the listed possibilities. It would seem that in both cases, applicants intended that these list be in the alternative. This is a NEW REJECTION. For appropriate methods of expressing alternative limitations in the claims see MPEP 2173.05(h).

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 44, 45, 47, 52-55, and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Nixon (Protein Eng 13: 323-327 (2000), of record). If the "stability" language were eliminated such that priority to the parent could be granted, this reference would still be a rejection under 102(a) as Provisional Application 60/182,283 does not provide support for "systemic" or "systemic" effects language. Thus any claim reciting the "systematic effects" language would only be granted the benefit of the date of the parent application, and not to the

provisional application. As such, this is a NEW REJECTION necessitated by the amendment to the claims on 5/25/05.

19. The claims are drawn to a method of assessing protein solubility comprising the steps of expressing a fusion protein in a host cell of a protein of interest and a first segment of a marker protein, which does not affect the solubility of the protein of interest, contacting the fusion protein with a second segment of the marker protein which can be structurally complemented by the first segment and determining structural complementation. The fusion can be C-terminal to the protein of interest. The marker protein can be an enzyme that can be β-galactosidase where the first segment can be the α-peptide and the second segment the ω-peptide. The assay is scored by comparing structural complementation to a negative control which can be a protein that improperly folds.

20. Nixon discloses a method for screening improvements in the solubility of a protein by fusing the protein to the α-fragment of β-galactosidase testing for solubility of the protein through blue/white screening (see page 325, first column, second full paragraph). The protein used by Nixon is a hybrid enzyme, where the α-fragment is C-terminally fused to the enzyme (page 324, first column second full paragraph). Indeed the assay of Nixon compares the structural complementation to protein that does not fold properly, as the assay of Nixon is specifically designed to find mutant so the hybrid enzyme that are more soluble. Thus, all assays are compared against the original protein which does not properly fold. Thus, Nixon anticipates each of claims 44, 45, 47, 52-55, and 57.

21. Claims 44, 45, 47, and 52-57 are rejected under 35 U.S.C. 102(b) as being anticipated by Wigley (Nat Biotech 19: 131-136 (2001), of record). This is a NEW REJECTION.

22. The claims are drawn as described above and additionally where the protein of interest can be CFTR. Wigley discloses a method for monitoring protein folding and solubility by monitoring structural complementation β-galactosidase (see whole article). The α-fragment is fused C-terminally to the protein of interest and measure for is ability to structurally complement the ω-fragment as compared to α-fusions that improperly fold. The exemplified protein is the NBD of CFTR. Thus, Wigley anticipates each of claims 44, 45, 47, and 52-57.

Response to Arguments

23. Applicant's argument, see page 8, lines 3-5 of the amendment filed 5/25/05, with respect to the scope of enablement rejection regarding the ability of the assay of the invention to asses stability have been fully considered and are persuasive. Further, the amendment to claim 44 reciting that the fusion protein is expressed in a host cells has obviated the rejection regarding the ability to perform the assay *in vitro*. The original rejection of claims 44-57 under 35 U.S.C. 112, first paragraph has been withdrawn. It is noted however, that the position is still held that the specification does not enable the skilled artisan to specifically assess stability without undue experimentation, only that a defect attributable to one of stability, folding, and or solubility can be assessed.

Terminal Disclaimer

24. The terminal disclaimer filed on 6/28/05 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of the patent from application 09/775,051 has been reviewed and is accepted. The terminal disclaimer has been recorded.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1633

DAVID GUZO
PRIMARY EXAMINER